Docket No.: 257546US0X PCT

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COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

RE: Application Serial No.: 10/510,371
Applicants: Hans-Ulrich PETEREIT, et al.
Filing Date: October 5, 2004
For: PH-SENSITIVE POLYMER
Group Art Unit: 1713
Examiner: BERNSHTEYN, MICHAEL

SIR:

Attached hereto for filing are the following papers:

Appeal Brief

Our credit card payment form in the amount of **$500.00** is attached covering any required fees. In the event any variance exists between the amount enclosed and the Patent Office charges for filing the above-noted documents, including any fees required under 37 C.F.R 1.136 for any necessary Extension of Time to make the filing of the attached documents timely, please charge or credit the difference to our Deposit Account No. 15-0030. Further, if these papers are not considered timely filed, then a petition is hereby made under 37 C.F.R. 1.136 for the necessary extension of time. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :

HANS-ULRICH PETEREIT, ET AL. : EXAMINER: BERNSHTEYN, MICHAEL

SERIAL NO: 10/510,371 :

FILED: OCTOBER 5, 2004 : GROUP ART UNIT: 1713

FOR: PH-SENSITIVE POLYMER :

APPEAL BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

The following is an Appeal of the Examiner's Final Rejection of September 26, 2006.

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(i) Real Party in Interest

ROEHM GMBH & CO. KG and the UNIVERSITE DE MONTREAL are the real parties in interest.

(ii) Related Appeals or Interferences

The Appellants are unaware of any related appeals or interferences that would directly affect, be directly affected by, or have a bearing on the Board's decision in this appeal.

(iii) Status of the Claims

Claims 1-12, 19 and 20 are on Appeal. Claim 1 (product) is the only independent claim. Claim 11 is a process claim depending from Claim 1.

Claims 13-18 have been withdrawn from consideration as being directed to a non-elected invention.

The Claims Appendix below provides a clean copy of the claims on appeal entered by the Amendment filed June 21, 2006.

(iv) Status of the Amendment

The Response filed on December 8, 2006 (after final rejection) does not amend the claims and the arguments therein have been considered, see the Advisory Action dated December 26, 2006. The Amendment filed June 21, 2006 contains the claims on appeal.

(v) Summary of the Claimed Subject Matter

The invention is directed to pH-sensitive polymer which has cytotoxic and membranolytic properties at pH values below 6.5 (i.e., in an acidic pH range occurring around endosomes inside of a cell) and which can be used as a carrier for pharmaceutical and biological molecules (specification, page 1). The introduction of pharmaceuticals or biomolecules into the cytoplasm requires membrane-destablizing agents which prevent the introduced substances which are engulfed in endosomes from being directed (trafficked) to the lysosomes where they are subject to degradation (specification, page 5, lines 30 *ff.*). A lysosome is an intracellular organelle containing digestive enzymes which degrade engulfed particles, such as viruses, bacteria or exogenous substance.

The polymers of the invention destabilize membranes at a pH around pH 6.5 which prevails in the endosomes (which would contain the exogenous pharmaceutical or biological molecule), but have no membranolytic effect on the external cytoplasmic membrane of the target cell at a pH value around pH 7.4 (specification, paragraph bridging pages 5-6). Thus, the claimed pH-sensitive polymers facilitate uptake of exogenous pharmaceutical or biological molecules without causing lysis of the target cell, but which affect an intracellular release of the pharmaceutical agent or biomolecule from the endosome inside the target cell. Thus, they prevent the pharmaceutical or biological molecule from being trafficked via the intact endosome to the lysosome for destruction.

Claim 1 is directed a pH-sensitive polymer comprising:

20 to 65% by weight of methacrylic acid units, and

80 to 35% by weight of units of C_1-C_{18}-alkyl esters of (meth)acrylic acid (original Claim 1, specification, page 7, lines 20 *ff.*);

wherein the pH-sensitive polymer has a molecular weight in the range from 1,000 to 50,000 g/mol (specification, page 7, lines 30-31),

does not contain transition metal complexes (specification, Table 1, page 25), and

brings about at least 60% haemolysis at pH 5.5, and less than 5% haemolysis at pH 7.4, at a concentration of 150 µg/ml in a cytotoxicity test with human red blood cells (original Claim 1, specification, page 12, lines 1-7).

Claim 11 is directed to a process for preparing a pH-sensitive polymer according to Claim 1, the process comprising:

free-radically polymerizing 20 to 65% by weight of methacrylic acid monomer units with 80 to 35% by weight of monomer units of C_1- to C_{18}-alkyl esters if (meth)acrylic acid in the presence of polymerization initiators and molecular weight regulators by block polymerization, bead polymerization, emulsion polymerization, group transfer polymerization (GTP), or atom transfer radical polymerization (ATRP) to form the polymer (original Claims 1 and 11, specification, page 14, lines 15 *ff.*),

discharging the polymer,

dissolving the polymer,

purifying the polymer and

drying the polymer (specification, page 15, lines 6-10).

(vi) Grounds of Rejection to be Reviewed on Appeal

Whether Claims 1-12 and 19-20 are unpatentable under 35 U.S.C. 103(a) as being obvious over Haddleton et al., U.S. Patent No. 5,804,632, in view of Rehmer et al., U.S. Patent No. 6,225,401.

The description and indefiniteness rejections have been withdrawn, see the Advisory Action dated December 26, 2006.

(vii) Argument(s).

Rejection—35 U.S.C. §103(a)

Claims 1-12 and 19-20 stand rejected under 35 U.S.C. 103(a) as being obvious over, Haddleton et al., U.S. Patent 5,804,632, in view of Rehmer et al., U.S. Patent No. 6,225,401. The Appellants respectfully request that this rejection be reversed.

> To establish a *prima facie* case of obviousness, three **basic** criteria must be met. First there must be some **suggestion or motivation**, either in the references themselves or in the knowledge generally available to one or ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must **be a reasonable expectation of success**. Finally, the prior art reference (or references when combined) must teach or suggest **all the claim limitations**. (M.P.E.P. 2143) (emphasis added).

Independent Claim 1 requires that the claimed pH-sensitive polymers have particular properties including non-toxicity (i.e., "less than 5% haemolysis at pH 7.4") and membranolytic properties at pH 5.5 (i.e., "at least 60% haemolysis at pH 5.5"). The pH-sensitive polymers of the invention are required to lack transition metal complexes, since these complexes are toxic to cells.

Haddleton was cited as generally disclosing preparing a low molecular weight polymer by free-radical polymerization using a transition metal complex, see e.g., Abstract and col. 5, lines 26-31. Haddleton is not particular about the monomer system used and col. 5, line 26 indicates that "any olefinically unsaturated monomer(s) which is amenable to (co)polymerization using CCT ("catalytic chain transfer") polymerization" can be used. Col. 6, lines 17 *ff.* refer to a range of 1-60 wt% acid comonomers and 99-40% non acid functional comonomers. If methacrylic acid is an acid comonomer, and if alkyl esters of (meth)acrylic acid are non acid functional comonomers, these ranges would appear to overlap the monomer content ranges of Claim 1. Methacrylate is mentioned in col. 6, line 26 as being a useful acid function

monomer and non acid functional comonomers like n-butyl methacrylate and n-butyl acrylate are mentioned on line 33 of col. 6. The Tables in cols. 13 and 14 describe mixtures of methyl methacrylate and methacrylic acid.

The Office has not shown that the Haddleton examples meet the content limitations of Claim 1. However, assuming *arguendo* that Haddleton discloses monomer mixtures of 20-65% by weight methacrylic acid + 80-35% by weight C_1-C_{18}-alkyl esters of (meth)acrylic acid as required by Claim 1, it does not disclose or suggest a mixture (A) lacking transition metal complexes or (B) having the properties required by Claim 1, that is, polymers that bring about at least 60% haemolysis of human red blood cells at pH 5.5, but less than 5% heamolysis at pH 7.4.

Rehmer is cited as disclosing a process for producing copolymers of acrylic and/or (meth)acrylic acid by emulsion polymerization instead of by CCT process used by Haddleton. The obviousness rejection is based on substituting the emulsion polymerization method of Rehmer for the CCT process of Haddleton for the purpose of obtaining the polymers of the invention which do not contain transition metal complexes and which have the pH-sensitive properties required by Claim 1. However, Haddleton and Rehmer even in combination do not suggest the invention for the following reasons.

(A) No motivation for omitting transition metal complexes. There is no motivation in Haddleton for omitting the transition metal complex, since this complex is required to control the molecular weight of the Haddleton polymers. The Haddleton polymers contain toxic transition metal ions, such as cobalt, which remain from a catalytic chain transfer (CCT) polymerization requiring the presence of these toxic metals, see Haddleton, col. 1, lines 50-52 and col. 3, lines 34-40. These remaining transition metals are toxic and would kill cells exposed to them. Similarly,

while Rehmer refers to emulsion polymerization, it too does not suggest omission of toxic transition metals. In fact, col. 3, line 23, refers to a process taking place in the presence of "polyvalent metal ions" such as iron and vanadium, thus teaching away from Claim 1 which requires the absence of transition metals. It is not surprising that Haddleton and Rehmer do not suggest omitting transition metal ions, because they have no reason to specifically exclude toxic metals, since the contemplated polymers are not disclosed for use in biological systems where the lack of transition metal toxicity would be required. Thus, Haddleton and Rehmer do not suggest omitting transition metal complexes.

(B) No motivation for selecting polymers which bring about at least 60% haemolysis at pH 5.5 and less than 5% haemolysis of human red blood cells at pH 7.4.

Page 5, last six lines of the final Official Action indicates that neither Haddleton or Rehmer disclose pH sensitive polymers that bring about at least 60% haemolysis at pH 5.5 and less than 5% haemolysis of human red blood cells at pH 7.4. However, the Official Action indicates that these properties are assumed to be inherent to the polymers of Haddleton and Rehmer, see lines 5-7 on page 6 of the final Official Action. The Official Action is not referring to a polymer exemplified by either Haddleton or Rehmer, but rather the class of polypeptides which could be made using the Rehmer emulsion polymerization process and the ingredients described by Haddleton.

If it is the Official position that all polymers produced using the monomers of Haddleton and the emulsion polymerization process of Rehmer would inherently have the properties required by Claim 1, then this position is clearly rebutted by the experimental data or record. Polymer S-100 (see Tables 1 and 2, pages 25 and 27 of

the specification) which falls does NOT have these properties even though it is composed of methacrylic acid and methyl methacrylate monomers.

If all of the polymers the Official Action is referring to do not have the properties required by Claim 1, then this element of the invention is not inherent to the prior art (nor as discussed below is it suggested by either Haddleton or Rehmer).

> To assert that a prior art reference inherently discloses an element of a claimed invention that Office must establish "that missing characteristic is necessarily present, or inherent, in the **single anticipating reference**", Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1268, 20 USPQ2d 1746 (Fed. Cir. 1991)(emphasis added).

Here, the final Official Action cannot establish that the pH-sensitivity limitations in Claim 1 are inherent to the class of prior art polymers because Polymer S-100 is a member of that class and does not have those properties. Moreover, the Office has not pointed out any exemplified polymer in either prior art reference that has these properties.

Haddleton and Rehmer fail to suggest the pH-sensitive polymers of the invention which bring about at least 60% haemolysis of human red blood cells at pH 5.5, but less than 5% heamolysis at pH 7.4. While page 7, line 4 of the final Official Action mentions the term "result effective variable" it does not indicate that the pH-sensitive properties required by the polymers of the invention are results-effective variables. It cannot, since pharmacological use of the Haddleton and Rehmer polymers is not contemplated. Thus, the argument with regard to optimizing a results effective is immaterial to the pH-sensitivity limitations in Claim 1.

Similarly, the prior art provides no reasonable expectation of success for polymers conforming to these limitations, since it does not contemplate the specific

pharmacological uses for the pH-sensitive polymers of the invention, e.g., to introduce pharmacological or biological agents into a cell.

Accordingly, since the prior art does not suggest the invention by (A) omitting toxic transition metal complexes and (B) selecting polymers that bring about at least 60% haemolysis of human red blood cells at pH 5.5, but less than 5% heamolysis at pH 7.4, nor provide any reasonable expectation of success for such polymers, the Appellants respectfully request that this rejection be reversed.

RELIEF REQUESTED

The Appellants respectfully request that the ground of rejection above be REVERSED.

Respectfully submitted,

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(viii) Claims Appendix

Claim 1 (Previously Presented): A pH-sensitive polymer comprising:

20 to 65% by weight of methacrylic acid units, and

80 to 35% by weight of units of C_1-C_{18}-alkyl esters of (meth)acrylic acid;

wherein the pH-sensitive polymer has a molecular weight in the range from 1,000 to 50,000 g/mol,

does not contain transition metal complexes, and

brings about at least 60% haemolysis at pH 5.5, and less than 5% haemolysis at pH 7.4, at a concentration of 150 μg/ml in a cytotoxicity test with human red blood cells.

Claim 2 (Previously Presented): The pH-sensitive polymer according to Claim 1,

wherein the pH-sensitive polymer comprises

40 to 60% by weight of methacrylic acid units and

60 to 40% by weight of ethyl acrylate units.

Claim 3 (Previously Presented): The pH-sensitive polymer according to Claim 1,

wherein the pH-sensitive polymer comprises

20 to 40% by weight of methacrylic acid units,

25 to 45% by weight of methyl acrylate units, and

25 to 45% by weight of ethyl acrylate units.

Claim 4 (Previously Presented): The pH-sensitive polymer according to Claim 1,

wherein the pH-sensitive polymer comprises

40 to 60% by weight of methacrylic acid units,

60 to 30% by weight of ethyl acrylate units, and

2 to 20% by weight of butyl methacrylate units.

Claim 5 (Previously Presented): The pH-sensitive polymer according to Claim 1,

wherein the pH-sensitive polymer comprises

40 to 60% by weight of methacrylic acid units,

60 to 40% by weight of ethyl acrylate units, and

0.1 to 2% by weight of units of a C_8- to C_{16}-alkyl ester of acrylate or methacrylate acid.

Claim 6 (Previously Presented): The pH-sensitive polymer according to Claim 1, wherein at a concentration of 0.03125 mg/ml the pH-sensitive polymer brings about in the MTT test with the mouse macrophage-like cell type J774A.1 (ATCC TIB-67) a percentage-value of cell survival of at least 25%, based on a 100% survival rate in the control experiment.

Claim 7 (Previously Presented): The pH-sensitive polymer according to Claim 1, wherein at a concentration of 0.03125 mg/ml the pH-sensitive polymer brings about in the LDH test with the mouse macrophage-like cell type J774A.1

(ATCC TIB-67) a LDH release-value of at not more than 40%, based on 100% cytolysis (toxicity) in the control experiment.

Claim 8 (Previously Presented): The pH-sensitive polymer according to Claim 1, wherein the pH-sensitive polymer is in the form of a conjugate or a complex with a pharmaceutically effective natural or synthetic biomolecule or an active pharmaceutical ingredient.

Claim 9 (Previously Presented): The pH-sensitive polymer according to Claim 1, wherein the pH-sensitive polymer is coupled to a conformation-altering agent.

Claim 10 (Previously Presented): The pH-sensitive polymer according to Claim 1, wherein the pH-sensitive polymer is a constituent of a complex crosslinked via nucleic acids after chemical modification.

Claim 11. (Previously Presented): A process for preparing a pH-sensitive polymer according to Claim 1, the process comprising:

free-radically polymerizing 20 to 65% by weight of methacrylic acid monomer units with 80 to 35% by weight of monomer units of C_1- to C_{18}-alkyl esters if (meth)acrylic acid in the presence of polymerization initiators and molecular weight regulators by block polymerization, bead polymerization, emulsion polymerization, group transfer polymerization (GTP), or atom transfer radical polymerization (ATRP) to form the polymer,

discharging the polymer,

dissolving the polymer,

purifying the polymer and

drying the polymer.

Claim 12 (Previously Presented): The process according to Claim 11, wherein the molecular weight regulator is dodecyl mercaptan and/or 2-ethylhexyl thioglycolate.

Claim 13 (Withdrawn): A medicinal substance comprising the pH-sensitive polymer according to Claim 1 as

a carrier for biomolecules or active pharmaceutical ingredients,

a conjugate for biomolecules or active pharmaceutical ingredients,

a complex for biomolecules or active pharmaceutical ingredients,

or as a constituent of microparticles, nanoparticles, liposomes, emulsions and/or lipid vesicles.

Claim 14 (Withdrawn): The medicinal substance according to Claim 13 wherein said biomolecules are selected from the group consisting of lipids, proteins, peptides, nucleic acids and mixtures thereof.

Claim 15 (Withdrawn): The medicinal substance according to Claim 13, wherein the active pharmaceutical ingredients are selected from the group consisting of analgesics, antiallergics, antirheumatics, antibiotics, antiinfectives, antiparkinson agents, antipsoriatics, antitumour agents, dermatologicals, gout remedies,

immunoregulators, gastrointestinal agents, neurotropic agents, opthalmologicals, cytostatics and mixtures thereof.

Claim 16 (Withdrawn): The medicinal substance according to Claim 13, wherein said medicinal substance is in a dermal, transdermal, parenteral, nasal, pulmonary, vaginal or oral dosage form.

Claim 17 (Withdrawn): The medicinal substance according to Claim 16 wherein said medicinal substance is effective in treating a disease selected from the group consisting of cancer, infections, cardiovascular disorders, arthritis, neurodegenerative disorders, genetically related enzyme-deficiency disorders, hepatitis B and C, mucoviscidosis, hypercholesteraemia, Down's syndrome, muscular dystrophy, autoimmune diseases, shingles and herpes, psoriasis, CMV retinitis, Crohn's disease, ulcerative colitis, diabetes and mixtures thereof.

Claim 18 (Withdrawn): The medicinal substance according to Claim 13 wherein said biomolecules are selected from the group consisting of oligonucleotides, nucleosides, antisense DNA, antisense RNA, nucleotides, toxins, immunotoxins, antibodies, fragments of antibodies and mixtures thereof.

Claim 19 (Previously Presented): The pH-sensitive polymer of Claim 1 which is produced by free radical polymerization of monomers in the presence of a polymerization initiator and molecular weight regulator by block, bead or emulsion polymerization.

Claim 20 (Previously Presented): The pH-sensitive polymer of Claim 1 which is not produced by catalytic chain polymerization (CCT), group transfer polymerization (GTP) or by atom transfer radical polymerization (ATRP).

(ix) Evidence Appendix

(None)